REMARKS

By this amendment, claim 7 has been amended and claim 8 has been cancelled without prejudice or disclaimer. Accordingly, claims 7 and 9-12 are currently pending in the application, of which claim 7 is an independent claim. New claims 21-33 have been added, of which claims 21 and 26 are independent.

The proposed amendment to claim 7 is solely proposed to more clearly define and distinctly claim the inventions defined herein. The amendment to claim 7 and newly added claims 21-30 are fully supported by the specification and original claims. It is submitted that no new matter has been introduced by the present amendment and entry of the same is respectfully requested. By these amendments, Applicant does not acquiesce to the propriety of any of the Examiner's rejections and does not disclaim any subject matter to which the Applicant is entitled.

In view of the above amendments and the following Remarks, Applicant respectfully requests reconsideration and timely withdrawal of the pending objections and rejections for the reason discussed below.

Title Objection

In the Office Action, the title of the invention was objected to as not being descriptive. The title has been amended to read

TREATMENT OF INTESTINAL EPITHELIAL CELL MALFUNCTION, INFLAMMATION OR DAMAGE WITH HEPATOCYTE GROWTH FACTOR

Accordingly, Applicant respectfully request withdrawal of the objection to the title.

Abstract Objection

In the Office Action, the abstract of the invention was objected to as not being descriptive. A new, replacement abstract as been provided. Accordingly, Applicant respectfully requests withdrawal of the objection to the abstract.

Rejections Under 35 U.S.C. §103

The Examiner has rejected claims 7-12 under 35 U.S.C. § 103(a). Specifically, the Examiner alleges that the claims are "obvious over Zushi (Am. J. Physiol. 270, G757-G762, 1996) and Ishii (JP 08231418) and Fukamachi (Biochem. Biophy. Research Communication, 205 (2), 1445-1451) and Halttunen (Gastroenterology, 111, 1252-1262, 1996)." Paper No. 2 at page 3. Applicant respectfully traverses.

To maintain a proper rejection under 35 U.S.C. § 103, the USPTO must meet four conditions to establish a *prima facie* case of obviousness. First, the USPTO must show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, the USPTO must show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant's disclosure. Third, the prior art must teach or suggest all the claim limitations. Fourth, if an obviousness rejection is based on some combination of prior art references, the USPTO must show the suggestion, teaching, or motivation to combine the prior art references.

The present invention is related to methods for treating a patient having intestinal mucosal damage by administering an effective dose of HGF to the patient. Claim 7 has been

amended to include a subject having "in vivo" conditions selected from the group consisting of Chronic Ulcerative Colitis, Crohn's Disease, necrotizing enterocolitis, severe acute gastroenteritis, chronix gastroenteritis, cholera, and chronic infections of the bowel. Claim 8 has been canceled because the elements of this claim have been included in claim 7.

Applicant respectfully contends that a *prima facie* case of obviousness has not been established because the cited prior art references fail to teach each and every element of the claimed invention. The Examiner alleges that Zushi et al., ("Zushi") "teach that HGF accelerates intestinal restitution (wound resealing)." *Id.* at page 3. Further, Zushi is cited for use of an *in vitro* cell culture model as being accepted in the art as a model of differentiation of intestinal and epithelial absorption. Zushi is inadequate as a primary reference because Zushi fails to teach or suggest each and every element of the claimed invention. Indeed, nowhere does Zushi teach or suggest that HGF will decrease mucosal damage in a patient having the "in vivo" conditions selected from the group consisting of Chronic Ulcerative Colitis, Crohn's Disease, necrotizing enterocolitis, severe acute gastroenteritis, chronic gastroenteritis, cholera, and chronic infections of the bowel. Further, nowhere does Zushi teach or suggest an effective dose of HGF. Therefore, Zushi neither teaches nor suggests all the elements required in claim 7 of the present application.

Next, Ishii is cited for the alleged teaching of using HGF to promote intestinal cell proliferation and motility and is useful for prevention or treatment of intestinal disease such as ulcerous colitis and inflammatory colitis. Ishii is directed to intestinal cell proliferation and motility using *in vitro* experiments. Applicant asserts that Ishii is inadequate as a secondary reference because it fails to remedy the deficiencies of Zushi. Nowhere does Ishii teach or suggest administering an effective dose of HGF to decrease mucosal damage in a patient.

Therefore, neither Zushi nor Ishii alone or in combination provides all of the elements required by claim 7 of the present application.

Fukamachi et al., ("Fukamachi") is cited for allegedly teaching that HGF stimulates growth of various types of cells including the growth of gastrointestinal epitheial cells. The results in Fukamachi were that HGF stimulated gastro-intestinal epithelial growth in primary cultures. These studies, however, were performed on fetal esophageal, gastric and duodenal cells which are genetically and functionally different from jejunal, ileal and colonic cells which are typically involved in the disease processes disclosed in the present application. Nothing in Fukamachi teaches decreasing mucosal damage in a patient having an "in vivo" condition selected from the group consisting of Chronic Ulcerative Colitis, Crohn's Disease, necrotizing enterocolitis, severe acute gastroenteritis, chronic gastroenteritis, cholera, and chronic infections of the bowel, by administering an effective dose of HGF. Therefore, Fukamachi when taken alone or in any combination with Zushi or Ishii fails to teach or suggest all the elements required in claim 7 of the present application.

Halttunen et al., ("Halttunen") is cited for its alleged teaching that the cell culture model used in the study is a comprehensive model of the intestine. The Examiner's interpretation is incorrect. Hulttunen reported an *in vitro* three-dimensional cell coculture model in which the intestinal crypt-like T84 epithelial cells organize and differentiate into a distinct phenotype when given fibroblast support. Halttunen was unable to produce a three dimensional cell model. Indeed, Halttunen acknowledges that *in vivo* studies of the intestinal mucosa are complex and difficult. Halttunen does not teach that the results of *in vitro* studies will provide the same results when performed *in vivo*. Further, the Examiner asserts that Hulttunen "demonstrate[s] that HGF stimulates proliferation of intestinal cells." Paper No. 2 at page 4. The Examiner is incorrect.

Halttunen stated that "HGF did not induce the organization of T84 cells but increased the proliferation rate instead." Gastroenterology, 111, 1260.

Halttunen is inadequate as a reference because it fails to teach or suggest each and every element of the claimed invention, and therefore fails to remedy the deficiencies of Zushi, Ishii, and Fukamachi. Nowhere does Halttunen teach or suggest decreasing mucosal damage in a patient having an "in vivo" condition selected from the group consisting of Chronic Ulcerative Colitis, Crohn's Disease, necrotizing enterocolitis, severe acute gastroenteritis, chronic gastroenteritis, cholera, and chronic infections of the bowel, by administering an effective dose of HGF. Therefore, Halttunen taken singly or in any combination with Zushi, Ishii and Fukamachi would not result in the presently claimed invention and does not support an obviousness rejection under 35 U.S.C. § 103(a). Accordingly, Applicant respectfully requests reconsideration and withdrawal of the present rejection.

The Examiner asserts that "taken together, the prior art demonstrates that HGF, in several cell culture models, stimulates proliferation of intestinal cells and augmentation of their motility." *Id.* at page 4. Applicant asserts that none of the cited references, alone or in any combination, teach using HGF to decrease mucosal damage in a patient having an *in vivo* condition by administering an effective dose of HGF whether *in vitro* or *in vivo*. Further, all of the cited references relate to *in vitro* studies and not one of the references teach or suggest that *in vitro* effects would correlate with *in vivo* effects. Indeed, Halttunen specifically acknowledges the difficulty and complexity of *in vivo* studies. Additionally, it is scientifically, clinically or logically inaccurate to suggest that the results of *in vitro* cell cultures would lead those of ordinary skill in the art to conclude that these results would provide evidence of benefit to the clinical disorders and/or diseases of the intestine that are induced by infection, inflammation,

and/or immunological disorders. *In vitro* studies use cells (typically immortalized) which are grown in nonphysiological conditions, not influenced by those morphologic circumstances present in intact intestine *in vivo* and without the pathologic conditions of infection, inflammation, or immunologic disorders that occur clinically.

The Examiner further asserts that it would be *prima facie* obvious "to one skilled in the pertinent art that such effect of HGF demonstrated on cellular level would *in vivo* translate into the increase in intestinal tissue mass and enhancement of intestinal functions, such as absorptive function." *Id.* at page 6. Applicant respectfully disagrees. The Examiner's allegation is without factual support. As discussed above, Zushi, Ishii, Fukamachi and Halttunen, either alone or in any combination, all fail to teach or suggest each and every element of the presently claimed invention. Therefore, a *prima facie* showing of obviousness has not been made. Furthermore, it is assumed by the Examiner that the only primary mechanism by which HGF is effective in inflammatory bowel disease is through cellular proliferation. The present invention indicates that HGF can reduce intestinal inflammation and damage.

The Examiner also asserts that the concentration of ranges is within the skill of the ordinary worker as a part of the process of normal optimization. Applicant respectfully disagrees. None of the prior art references cited by the Examine, which only relate to *in vitro* studies, teach or suggest the effective HGF dosage range of the present invention. It is inaccurate to suggest that the results of *in vitro* cell culture studies could be simply extrapolated by one skill in the art to arrive at the effective HGF dosage ranges of the present invention that would result in a decrease of intestinal mucosal damage. Accordingly, the effective HGF dose would not have been obvious to one skilled in the art.

Finally, it is relevant to note that the Examiner uses the same prior art references to reject the claims of the present application as those that were used to reject the claims in the U.S. Patent No. 5,972,887 ('887 patent), which are related to patients with inadequate intestinal absorption. The rejections of the '887 patent were withdrawn by the Examiner because the cell culture data could not be extrapolated to mucosa undergoing the process of intestinal adaptation. Similarly, cell culture data cannot be extrapolated to the *in vivo* histology, pathophysiology or the results obtained with HGF in a model of immunologically induced inflammatory bowel disease. Accordingly, the *in vivo* conditions have been incorporated into claim 7 of the present application.

Therefore, based upon the above remarks, Applicant submits that claim 7 is in condition for allowance. Claims 9-12 are all dependent claims that depend either directly or indirectly from claim 7 and are likewise allowable.

Rejection under Obviousness - Type Double Patenting

The Examiner has rejected the claims 7-12 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-18 of U.S. Pat. No. 5,972,887. Applicant respectfully requests that this rejection be held in abeyance until allowable claims are indicated by the Examiner. Subsequently, if necessary, Applicants will file a terminal disclaimer to overcome the rejection.

CONCLUSION

Applicant believes that a full and complete response has been made to the pending Office Action and respectfully submits that all of the stated objections and grounds for rejection have been overcome or rendered moot. Accordingly, Applicant respectfully submits that all pending claims are allowable and that the application is in condition for allowance.

Should the Examiner feel that there are any issues outstanding after consideration of this response; the Examiner is invited to contact the Applicant's undersigned representative at the number below to expedite prosecution.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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Abstract Replacement Sheet

ABSTRACT

The present invention relates to a method and composition for treating a patient having a condition characterized as inflammatory bowel disease with an effective dose of HGF. Inflammatory bowel disease as defined by the present invention, includes Chronic Ulcerative Colitis, Crohn's Disease, necrotizing enterocolitis, severe acute gastroenteritis, chronic gastroenteritis, cholera, chronic infections of the bowel, immunologic disorders affecting the intestine, immunodeficiency syndromes affecting the intestine, and HIV. Mucosal damage and histologic lesions are reduced by administering an effective dose of HGF to patients suffering from the same. Specifically, the effective dose of HGF is in a range of about 30 μg/kg body weight/day to about 300 μg/kg body weight/day. HGF may be administered to the patient lumenally or systemically.